apoptosis factor-1 and -2 (AP-1 and AP-2), mdm2, and proteins and receptors that share 20% or more sequence identity to these.

[0119] The biological target molecule of interest can be chosen such that it possesses or is modified to possess a chemically reactive group which is capable of forming a covalent bond with members of a library of small organic molecules. For example, many biological target molecules naturally possess chemically reactive groups (for example, amine groups, thiol groups, aldehyde groups, ketone groups, alcohol groups and a host of other chemically reactive groups; see below) to which members of an organic molecule library may interact and covalently bond. In this regard, it is noted that polypeptides often have amino acids with chemically reactive side chains (e.g., cysteine, lysine, arginine, and the like). Additionally, synthetic technology presently allows the synthesis of biological target molecules using, for example, automated peptide or nucleic acid synthesizers, which possess chemically reactive groups at predetermined sites of interest. As such, a chemically reactive group may be synthetically introduced into the biological target molecule during automated synthesis.

[0120] Moreover, techniques well known in the art are available for modifying biological target molecules such that they possess a chemically reactive group at a site of interest which is capable of forming a covalent bond with a small organic molecule. In this regard, different biological molecules may be chemically modified (using a variety of commercially or otherwise available chemical reagents) or otherwise coupled, either covalently or non-covalently, to a compound that comprises both a group capable of linking to a site on the target molecule and a chemically reactive group such that the modified biological target molecule now possesses an available chemically reactive group at a site of interest. With regard to the latter, techniques for linking a compound comprising a chemically reactive group to a target biomolecule are well known in the art and may be routinely employed herein to obtain a modified biological target molecule which comprises a chemically reactive group at a site of interest.

[0121] IV. Microarray Hybridization

[0122] In accordance with embodiments of the present invention, systems and methods are provided for facilitating interactions between molecules bound to a microarray substrate surface and molecules in a target liquid. Various systems and methods described below may not be limited to hybridization processes, but can also be applicable for other molecular interactions, such as, for example, associations, complexing, reactions, ionic and/or hydrogen bonding, bonding between molecules.

[0123] To minimize consumption of sample fluid, the hybridization chambers in existing hybridization systems are normally several centimeters across in the XY plane but tens of micrometers in thickness (Z). Liquids contained in such a chamber may exhibit typical microfluidic behavior because the small Z dimension causes the surface to be tension dominant. If no flow is introduced in the chamber, the liquid-probe mixing can only be achieved through diffusion, which is very slow and practically impossible across such a large XY dimension. Because of this, each probe only hybridizes with target molecules in a small volume near the probe in a "static hybridization" condition, which significantly reduces the detection sensitivity. To improve the sensitivity, a "dynamic hybridization" condition can be created where the sample liquid is driven to mix thoroughly with the probe array.

[0124] A. Hybridization Apparatus with Movable Substrate or Cover

[0125] The rate of hybridization can be increased by introducing active mixing during hybridization by creating relative motion between a substrate and a cover of a hybridization apparatus. An array hybridization apparatus incorporating a movable substrate or a movable cover includes a substrate and a cover, wherein the substrate and/or the cover are movable relative to each other. The substrate can be in the form of a flat substrate slide on which an array of probes is deposited. The cover can be a cover slip which mates with the substrate slide to form a hybridization chamber.

[0126] 1. Target Liquid Confinement

[0127] A target liquid added to an array hybridization apparatus between a substrate slide and a cover slip may be confined by using a surface tension differential created on the surface of the substrate slide and/or the cover slip. The surface of the substrate slide can have a coating to form a hydrophilic region surrounded by hydrophobic region. The hydrophilic region contains an array of probes. Surface energies between the hydrophobic and hydrophilic coating confine the target liquid within the hydrophilic region. The substrate slide can be designed to have multiple hydrophilic regions separated or surrounded by hydrophobic regions so that multiple liquid samples and multiple probe arrays can be applied to the same substrate slide without cross-contamination. In other embodiments, the target liquid can be contained on the substrate using a hydrophobic region surrounding an untreated region. Similarly, the target liquid can be contained on a hydrophilic region surrounded by an untreated region.

[0128] As used herein, the term hydrophobic is used to describe a surface or coating which forms a contact angle of greater than 90° when a droplet of water is deposited thereon. The term hydrophilic is used to describe a surface or coating which forms a contact angle of less than 90° when a droplet of water is deposited thereon.

[0129] Numerous methods are available for forming the hydrophilic and hydrophobic coatings or materials used in embodiments of the present invention. For example, various methods are described in U.S. patent application Ser. No. 10/080,274, entitled "Method and Apparatus Based on Bundled Capillaries for High Throughput Screening," by Shiping Chen et al., filed Feb. 19, 2002, incorporated by reference herein in its entirety.

[0130] In accordance with one embodiment, masking technology is utilized to prepare localized areas on the surface for selective hydrophilization. **FIG. 7** shows a process for fabrication using a negative mask. In this method, the entire surface of a substrate is first functionalized with a hydrophobic ("1") chemistry. Next a mask is placed on the substrate surface and the hydrophobic chemistry is removed from the exposed regions using, e.g., a chemical removal process. The exposed (and stripped) regions are then functionalized with a hydrophilic chemistry ("2"). The localized hydrophilic regions can alternatively be formed using a positive masking process.